

10 July 2008

## Neuropharm

Year End	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	PE (x)	Yield (%)
06/06	0.0	(0.3)	(6.6)	0.0	N/A	N/A
06/07	0.0	(2.7)	(13.8)	0.0	N/A	N/A
06/08e	0.0	(6.1)	(18.3)	0.0	N/A	N/A
06/09e	0.0	(6.5)	(19.5)	0.0	N/A	N/A

Note: \*PBT and EPS are normalised, excluding goodwill amortisation and exceptional items

### Investment summary: Fragile X results soon

Results of Phase II studies of Neuropharm's programmes for Fragile X syndrome are due to be presented at a scientific meeting later this month. Recruitment into the SOFIA trial of NPL-2008 for autism is going well, with clinical phase expected to complete around the year-end. A potential rolling NDA filing of NPL-2008 could start in early Q4, which would complete with the submission of the clinical data. NPL-2008 could become the first drug approved for treating a core symptom of autism and, with potential for fast-track review, this is possible by Q4 2009.

### Data at 11th International Fragile X Conference

Results of pilot studies of NPL-2005 and NPL-2009 are due to be presented at the 11th International Fragile X Conference, the leading scientific meeting in this disease area. Submissions are also planned for journal publications.

### SOFIA study

Neuropharm has increased the number of centres involved in the SOFIA study from 12 to 19 to gain broader geographic coverage and increase awareness of NPL-2008 among autism specialists and KOLs. This has slowed recruitment slightly, although the clinical phase is still expected to complete by the year end.

### Paediatric OCD

The paediatric OCD trial has been closed, part-recruited, and is expected to render data during Q4. We understand, however, that Neuropharm is already facilitating further studies of the drug with an independent investigator in an adult population.

### Valuation: rNPV of £250m

We are maintaining our risk-adjusted NPV valuation of £250m, which represents a multiple of Neuropharm's EV. Neuropharm's share price has held up well in the turbulent market conditions of recent months, which we would suggest is a reflection of its clear strategy, near-term catalysts and strong balance sheet.

Price 171.5p  
Market Cap £54m

#### Share price graph



#### Share details

Code NPH  
Listing AIM  
Sector Pharmaceuticals & Biotech  
Shares in issue 31.5m

#### Price

52 week High 191p Low 140p

#### Balance Sheet as at 30 June 2008\*

Debt/Equity (%) N/A  
NAV per share (p) 28.0  
Net cash (£m) 10.8

\* Estimated

#### Business

Neuropharm is an emerging speciality pharmaceutical group focused on the development of medicines for the treatment of neuro-developmental disorders.

#### Valuation

	2007	2008e	2009e
P/E relative	N/A	N/A	N/A
P/CF	N/A	N/A	N/A
EV/Sales	N/A	N/A	N/A
ROE	N/A	N/A	N/A

#### Revenues by geography

	UK	Europe	US	Other
	100%	0%	0%	0%

#### Analyst

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## Background

Neuropharm is an UK-based emerging speciality pharmaceutical company focused on CNS conditions, in particular neuro-developmental disorders affecting children (autism, Fragile X syndrome and paediatric obsessive compulsive disorder). Its principal product is a novel formulation of fluoxetine (a widely used, off-patent SSRI antidepressant) for the treatment of the core symptoms of autism using Catalent Pharma Solutions' Zydys technology. The Zydys formulation (which melts in the mouth in less than three seconds) is thought to be highly suitable for administration of drugs to autistic children.

The company has orphan drug designation for three programmes and intends to establish its own sales force in the US, allowing it to capture a significantly greater proportion of the value of its products than is normally the case for biotech companies.

The current status Neuropharm's R&D pipeline is summarised in Exhibit 1 below.

### Exhibit 1: Neuropharm R&D Summary

Project	Indication	Development stage/notes
NPL-2008 (Zydys Fast-melt formulation of fluoxetine)	Autism	Recruitment into the 128-patient, 14-week Phase III SOFIA study is well underway. The trial design allows dosing at between 2-18mg with flexible titration up to minimum effective dose (MED). Completion of the clinical phase is expected by the year end. Planned rolling NDA expected to start in early Q4 (with the CMC package) and complete with clinical data. FDA fast-track status and priority review means US launch remains possible in Q409. Open-label phase will continue into 2010, examining IQ. Potential out-licensing opportunity in Europe. US orphan drug designation held. Plans for submission in the EU are being progressed. <b>Commercial agreements.</b> Original clinical trial data and orphan drug designation acquired from Mount Sinai School of Medicine in return for a 5% royalty on US net sales. Agreement with Catalent Pharma Solutions covering the Zydys technology provides for transfer prices and a profit share equivalent to 10% of gross margin for the first three years, reducing to 3% in year seven and thereafter.
NPL-2005 (valproate)	Fragile X syndrome (behavioural symptoms)	Pilot Phase II study in 10 patients complete. Results to be presented at forthcoming International Fragile X conference. Strategy is to develop a novel formulation in this indication (valproate is a marketed, off-patent anticonvulsant used for epilepsy and bipolar disorder). US orphan drug designation held.
NPL-2009 (fenobam)	Fragile X syndrome	12-patient, open-label dose-escalation Phase II study completed of 50mg-150 mg single dose in adults (of both sexes). Primary endpoint is safety and PK, with examination of efficacy using prepulse inhibition tests and continuous performance tasks. Results to be presented at the International Fragile X conference. US orphan drug designation held. <b>Commercial agreements.</b> Preclinical data acquired from FRAXA in return for a 3% royalty on net sales; right of reference to the original IND from J&J in return for a 3% royalty interest for 10 years.
NPL-2003 (undisclosed)	Paediatric OCD	Phase II study was closed, part-recruited, with data expected to be reported in Q4. However, Neuropharm has already agreed to facilitate further studies through an independent investigator in the adult population. Active agent is a marketed antibiotic.

Source: Edison Investment Research

## Investment summary: NPL-2008 data are key

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Recruitment into the SOFIA Phase III trial of NPL-2008, on which Neuropharm's investment case critically depends, is progressing well and the study is expected to complete its clinical phase by the end of the year. However, before this Neuropharm will report data from its earlier-stage Phase II programmes in Fragile X syndrome (which will be published at a scientific meeting later this month) and paediatric OCD. Neuropharm also expects to provide a regulatory update on NPL-2008 in July, when it should have some visibility on the CMC (chemistry, manufacturing and controls) package and the timetable for its submission of its planned rolling NDA. Preliminary results for the year to 30 June will also be published in September/October.

### SOFIA study

The NPL-2008 trial, codenamed SOFIA (Study Of Fluoxetine In Autism), is targeting an enrolment of 128 patients. The trial is double blind and runs for 14 weeks, with an open-label extension. Patients will be titrated to one of three doses (2mg, 9mg or 18mg/day) to try to maintain an at least 25% reduction in CYBOCS-PDD, which is assessed at two weekly intervals. This means patients will be exposed to the lowest dose which provides a clinically meaningful improvement in their symptoms. Children can be recruited from five years old and above and the mean age is likely to be around eight. The primary endpoint is a measurement of repetitive behaviours (a core symptom of autism) using the Children's Yale-Brown Obsessive Compulsive Scale modified for pervasive developmental disorders (CYBOCS-PDD).

Neuropharm has increased the number of centres in the SOFIA study from 12 to 19 in order to gain a broader geographic coverage in the US and build awareness of NPL-2008 among a larger number of autism specialists and key opinion leaders. This has slowed recruitment slightly, but management still expects to complete the blinded phase around the end of this year (data will become available shortly thereafter). Neuropharm has applied for permission to use a rolling NDA, which is likely to start in early Q4 (with the CMC package) and will complete with the clinical data.

### Autism

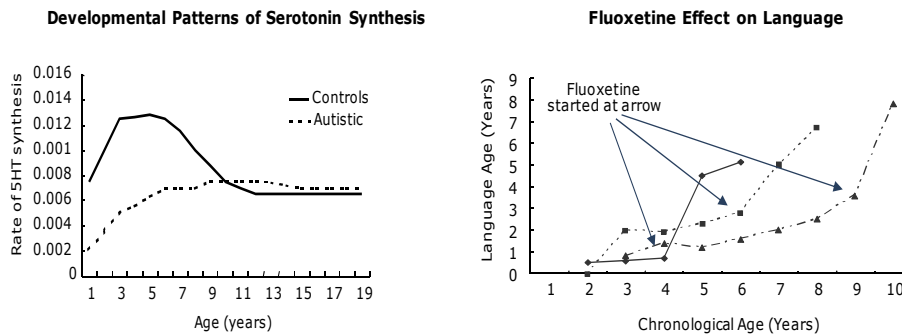
Autism, and the broader autistic/autism spectrum disorder, is a developmental disorder first seen in children from around the age of three years and is characterised by impairment in three core domains: social impairment, speech/communication deficits, and repetitive behaviour/compulsivity. These symptoms frequently co-exist with others including social phobia, ADHD, excessive/repetitive language disorders, EEG abnormalities, OCD and impulsivity/aggression.

The prevalence of autism is around 0.6% of the population (higher in boys, perhaps one in 100). A little under 1% of the population meets criteria for the broader autism phenotype (autism spectrum disorder), which includes Asperger's syndrome and PDD-NOS (pervasive developmental disorder, not otherwise specified).

Autistic children appear to exhibit much lower levels of serotonin relative to normal children of the same age (at least up to around nine years), which is shown in the left hand chart in Exhibit 2. The thesis underlying the development of NPL-2008 is therefore that if serotonin levels can be

corrected by drug therapy (ie by a serotonin re-uptake inhibitor such as fluoxetine), the symptoms of the condition will improve. This is supported by case data showing a marked improvement in language age (and a reduction in the language age deficit relative to chronological age) in children after initiation of fluoxetine (shown in the right hand chart).

### Exhibit 2: Serotonin and autism



Source: Chugani et al., (1999) *Ann Neurol* 45 287

Source: DeLong et al., (1998) *Dev Med Child Neurol* 40 551

Source: Neuropharm

A number of trials (mostly open-label) have been conducted with SSRIs in autism and autism spectrum disorders, including with citalopram, escitalopram, fluvoxamine and sertraline, most of which have demonstrated some improvement in global functioning and symptoms associated with anxiety and repetitive behaviour. Fluoxetine is considered to be the most suitable of these for a number of reasons and is the only drug to have shown positive results in double-blind study in children and adolescents with autism (from age five). It is also the only SSRI specifically indicated for use in children (aged eight and over) for depression and OCD. By contrast, paroxetine (Seroxat, GSK) is specifically contra-indicated in children and adolescents. (Other SSRIs such as fluvoxamine (Luvox, Solvay) and sertraline (Zoloft, Pfizer) are, however, often used off-label in children for OCD).

Neuropharm collaborator Dr Eric Hollander of the Seaver Autism Centre at Mount Sinai School of Medicine in New York conducted three clinical trials with fluoxetine in autism. These include a Phase IIb trial (in children and adolescents) and a Phase III trial (in adults), which were funded by FDA Office of Orphan Drug Development. The Phase IIb study measured an 8% reduction in the CYBOCCS score on fluoxetine, versus a 3% increase on placebo, a statistically significant difference ( $p=0.039$ ). However, these studies were conducted at a single site and in older children and, it is also thought, the doses used were too high (as the developing brains of young autistic children are forced to compensate for low levels of serotonin by becoming much more sensitive to the neurotransmitter). The intention is therefore to initiate treatment at an earlier age and with a lower, more carefully titrated low dose.

To our knowledge, NPL-2008 is the only product in development aimed at treating a core symptom of autism (i.e. one used for its diagnosis). There are currently no products specifically approved for treating autism, although Risperdal is indicated for treating irritability associated with the condition. A variety of drugs are used off-label for some of the co-morbidities associated with the condition.

Exhibit 3 summarises other products currently in trials for the treatment of symptoms/co-morbidities associated with autism.

**Exhibit 3: Other products in development for core symptoms or co-morbidities autism**

Note: NIMH = National Institute of Mental Health; part of the NIH.

Product	Company	Development stage/clinical trials/notes
Risperdal (risperidone)	J&J	Licensed for the treatment of irritability and associated behaviour in autistic children. 93-patient, Phase IV study to evaluate irritability and related behaviours of two different fixed dose levels in children or adolescents with autism for six weeks, with a 26-week extension (results: Sept 2009).
Invega (paliperidone)	J&J	30-patient eight-week, open-label study examining aggression, self-injury and irritability in adolescents and young adults with autism (results: Aug 2009).
Abilify (aripiprazole)	Bristol-Myers Squibb/Otsuka	300-patient, 52-week (flexible dose 2mg to 15mg) in children and adolescents with autistic disorders (completion June 2009). 30-patient, Phase II study on behaviours and development associated with ASD (completion: Jan 2009). 15-patient long term Phase II study (results: Dec 2008).
Daytrana (methylphenidate patch)	Shire	Investigator-sponsored 20-pt Phase II open-label pilot study for treatment of attention and behavioural symptoms in children with autism spectrum disorders (results: Dec 2008).
Strattera (atomoxetine)	Lilly	100-patient, eight-week Phase IV study for symptoms of ADHD in children and adolescents with ASD (completion: May 2010). NIMH-sponsored 86-patient, Phase III study in children with ADHD symptoms associated with autism, Asperger's syndrome and PDD-NOS (completion: Jul 2012).
Intranasal oxytocin	Various (Novartis)	Investigator-sponsored Phase II to evaluate improvement of mood and social functioning in adults with autism.
Oxcarbazepine	Various generic	Investigator-sponsored 12-week, 20-patient study to assess the effectiveness in childhood/adolescent autism.
Zyprexa /olanzepine	Lilly (Zydis formulation) /generic oral.	78-patient Phase II study examining effect on disruptive behaviours associated with autism in children aged three to 12 years. The first six weeks are double-blind; the second six weeks all patients are on drug (results: June 2009). NIMH-sponsored long-term Phase II/III study (results: Sept 2009).
citalopram	Various/generic	NIMH-sponsored 12-week Phase II study in 149 children. Completed but unpublished.
Naltrexone	Various/generic	Investigator-sponsored 50-patient study to examine effect of low-dose naltrexone on children with ASD looking at social functioning and language.

Source: Edison Investment Research

## Intellectual property

Neuropharm's IP on NPL-2008 consists of the US orphan drug designation, the IP covering the Zydis formulation (covered by patents held by Catalent) and the data exclusivity/protection afforded to regulatory filings (generally five years in the US and 10 years in Europe).

The US orphan drug designation (ODD; which becomes orphan drug status on approval) provides seven years' market exclusivity (i.e. it prevents the FDA granting approval to any competing formulation of fluoxetine for autism during this period), as an incentive for development. This ODD is a little unusual since the current estimate of the number of patients with autism in the US (at around 1m) far exceeds the 200,000 maximum specified in the legislation. However, at the time it was granted, the number of patients was thought to be less than 200,000. This makes it highly unlikely that any competing product would ever be able to gain an ODD for autism.

The mg/day dose likely to be used in autism (possibly in the range from 2-18mg) is much lower than the normal dose used in treating depression or OCD (10-80mg, averaging 60mg), making the off-label use of divided generic tablet versions difficult. Liquid formulations are available, but at a concentration of 20mg/5ml, they would have to be diluted or given in very small amounts to achieve the low doses thought necessary for autism. Nonetheless, a relatively high proportion of autistic patients in the US are understood to be treated off-label with versions of fluoxetine.

## Pricing will be key

An important factor to the commercial success of NPL-2008 will be pricing particularly in relation to dose, as there is likely to be a wide variation between the lowest and highest doses (up to nine times). It seems likely, therefore, that Neuropharm will have to use a complex pricing model in respect to dose, so as to keep the per-patient cost within a narrower range. The key will be for it to find a pricing structure that is acceptable to all patients and healthcare providers. However, feedback from key opinion leaders suggests there is strong support for a premium-priced product.

For the purposes of modelling, we have assumed that Neuropharm prices NPL-2008 to achieve an average price of \$6 per patient per day (or \$2,000 per patient per year). On this basis, we believe it could achieve a high penetration rate among young autism patients (possibly up to 50%, although our valuation is generated using a lower figure).

There are some 300 key opinion leaders and a further 3,600 specialists (child psychiatrists, child neurologists and developmental paediatricians) in the US, which Neuropharm believes could be addressed with a US sales force of 20-25 reps. Neuropharm intends to establish the US sales infrastructure in mid 2009, as the product nears approval.

## Earlier stage programmes - fragile X, paediatric OCD

Data from two small pilot studies for Fragile X syndrome are due to be published at the International Fragile X Conference in St Louis (26-31 July): these are of NPL-2005, which has now been disclosed to be valproate, and NPL-2009 or fenobam, an off-patent NCE that has been studied but not approved in another indication.

The presentation on NPL-2005 will be made by Professor Giovanni Neri of the University Cattolica in Rome, Italy and the presentation on NPL-2009 will be made jointly by Professor Randi Hagerman of the MIND Institute at UC Davis and Professor Elizabeth Berry-Kravis of Rush-Presbyterian-St. Luke's Medical Center in Chicago, in a plenary session.

Fragile X syndrome is, as the name suggests, a genetic disorder caused by a faulty X-chromosome (a mutation of the FMR1 gene). Although rare, it is the largest cause of inherited mental retardation; it affects around one in every 3,600 males and one in 4,000-6,000 females. Boys are usually more severely affected than girls (who would have one faulty and one normal X chromosome). Its features include mental impairment, ranging from learning disabilities to mental retardation, attention deficit and hyperactivity, anxiety, unstable mood and autistic behaviour. While most Fragile X boys have mental retardation, only 30-50% of girls have significant intellectual impairment. Emotional and behavioural problems are, however, common to both sexes. About 20% of boys with Fragile X meet the criteria for autism. There is currently no approved treatment for Fragile X syndrome.

Finally, a pilot study of NPL-2003, an undisclosed marketed antibiotic for paediatric obsessive compulsive disorder, is due to report in Q4. The trial was closed having recruited a portion of the expected 20 patients. However, we understand that Neuropharm has already agreed to facilitate another study to be conducted by an independent investigator in the adult population.

## Valuation

We are maintaining our risk-adjusted NPV valuation of £250m, as published in the February outlook note, which we compare with the EV (currently £44m). The assumptions behind this valuation are set out in Exhibit 4.

### Exhibit 4: Edison valuation case assumptions

Note: Potential market value for orphan indications based on estimates of 150,000 patients; \* sales at peak market share, three years into launch.

Product/indication	Status	Prob. of success	Launch year	Peak market share	Est. peak sales* (\$m)
NPL-2008/autism – US	Phase III	75%	Q4 2009	30%	\$575m
NPL-2008/autism – EU	Phase III	75%	2012	10%	\$120m
NPL-2005/Fragile X	Phase II	25%	2012	10%	\$40m
NPL-2009/ Fragile X syndrome	Phase II	20%	2012	10%	\$40m
NPL-2003/ paediatric OCD	Phase II	25%	2012	10%	\$75m

Source: Edison Investment Research

## Financials

Our model indicates Neuropharm will record an operating loss of around £7m for the year to 30 June, reflecting spending on its programmes, and will end the year with cash of £10.6m. Full-year results are due to be reported in September/October.

The company raised £20m gross (£18.2m net) in its 2007 AIM listing. Management anticipates it will have funds to bring NPL-2008 to the US market. Neuropharm operates with a low fixed cost base and would not need to incur most of the costs in establishing its US salesforce until it can be reasonably confident of approval in mid-2009.

**Exhibit 3: Financials**

Note: 2006 was the year of incorporation. US launch of NPL-2008 is possible in FY2010, although forecasts do not anticipate this, pending the outcome of the SOFIA study.

Year end 30 June	£'000	2006 IFRS	2007 IFRS	2008e IFRS	2009e IFRS	2010e IFRS
<b>PROFIT &amp; LOSS</b>						
<b>Revenue</b>		0	0	0	0	0
Cost of Sales		0	0	0	0	0
Gross Profit		0	0	0	0	0
<b>EBITDA</b>		(277)	(3,006)	(7,011)	(6,904)	(3,353)
<b>Operating Profit (before GW and except.)</b>		(277)	(3,009)	(7,016)	(6,911)	(3,361)
Intangible Amortisation		0	(3)	(3)	(3)	(2)
Exceptionals		0	0	0	0	0
Other		(86)	(544)	(150)	(550)	(550)
<b>Operating Profit</b>		(363)	(3,556)	(7,169)	(7,464)	(3,913)
Net Interest		0	320	900	400	200
<b>Profit Before Tax (norm)</b>		(277)	(2,689)	(6,116)	(6,511)	(3,161)
<b>Profit Before Tax (FRS 3)</b>		(363)	(3,236)	(6,269)	(7,064)	(3,713)
Tax		0	0	350	350	350
<b>Profit After Tax (norm)</b>		(277)	(2,689)	(5,766)	(6,161)	(2,811)
<b>Profit After Tax (FRS 3)</b>		(363)	(3,236)	(5,919)	(6,714)	(3,363)
Average Number of Shares Outstanding (m)		4.2	19.5	31.5	31.5	31.5
EPS - normalised (p)		(6.6)	(13.8)	(18.3)	(19.5)	(8.9)
EPS - FRS 3 (p)		(8.7)	(16.6)	(18.8)	(21.3)	(10.7)
Dividend per share (p)		0.0	0.0	0.0	0.0	0.0
<b>BALANCE SHEET</b>						
<b>Fixed Assets</b>		0	59	66	71	75
Intangible Assets		0	47	44	41	39
Tangible Assets		0	12	22	30	36
Investments		0	0	0	0	0
<b>Current Assets</b>		570	18,109	11,429	5,508	2,339
Stocks		0	0	0	0	0
Debtors		101	458	800	800	800
Cash		469	17,651	10,629	4,708	1,539
<b>Current Liabilities</b>		(146)	(1,365)	(2,600)	(2,000)	(2,000)
Creditors		(146)	(1,365)	(2,600)	(2,000)	(2,000)
Short term borrowings		0	0	0	0	0
<b>Long Term Liabilities</b>		0	(101)	(101)	(101)	(100)
Long term borrowings		0	0	0	0	0
Other long term liabilities		0	(101)	(101)	(101)	(100)
<b>Net Assets</b>		424	16,702	8,794	3,478	314
<b>CASH FLOW</b>						
<b>Operating Cash Flow</b>		(232)	(2,144)	(7,907)	(6,307)	(3,355)
Net Interest		0	320	900	400	200
Tax		0	0	0	0	0
Capex		0	(15)	(15)	(15)	(14)
Expenditure on intangibles		0	0	0	0	0
Acquisitions/disposals		0	0	0	0	0
Financing		701	19,021	0	0	0
Dividends		0	0	0	0	0
Net Cash Flow		469	17,182	(7,022)	(5,922)	(3,169)
<b>Opening net debt/(cash)</b>		0	(469)	(17,651)	(10,629)	(4,708)
HP finance leases initiated		0	0	0	0	0
Other		0	0	0	0	0
<b>Closing net debt/(cash)</b>		(469)	(17,651)	(10,629)	(4,708)	(1,539)

Source: Edison Investment Research

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